APPENDIX B:
BACKGROUND FOR DEVELOPMENT OF AN AD HOC EXPOSURE INDEX FOR ASBESTOS

The asbestos exposure index recommended for supporting risk assessment in this report (i.e. the interim index, C_{asb}, as defined by Equation 7.13) represents a compromise. The index preserves most of the important features of the optimum exposure index (Equation 7.12) that is recommended based on the results of our supplemental literature review (Chapter 7) combined with our formal statistical re-analysis of the animal inhalation studies conducted by Davis et al. (Section 7.4.3). These features include:

- a maximum structure width similar to;
- the same minimum structure length as; and
- the same analytical requirements for obtaining the required counts as

the optimum index. However, due to the limitations in the published size distributions available for re-evaluating the human epidemiology studies (Section 6.2.4.2), the longest category of structures had to be shortened from that incorporated in the optimum index (40 µm) to 10 µm, which is incorporated in the interim index (Section 7.5).

Nevertheless, we expect C_{asb} to provide somewhat conservative (in a health protective sense) estimates of asbestos exposure because we believe that:

- the minimum length for the structures included in C_{asb} (5 µm) is sufficiently short to capture the range of structures that contribute both to lung cancer and to mesothelioma in humans;

- the maximum width for the structures included in C_{asb} (0.5 µm) is greater than the greatest width observed to contribute in our formal analysis of the Davis et al. studies and is expected to be sufficiently wide to capture the bulk of the range of structures that contribute both to lung cancer and to mesothelioma. Importantly, contributions from thicker, complex structures are also included because the counting rules adopted to provide measurements for generating estimates of C_{asb} require that the thinner components of these complex structures be individually enumerated and included in the overall count of structures; and

- the weighting factors incorporated in Equation 7.13 are conservative (in a health protective sense) in that they are adopted directly from the optimum exposure index (Equation 7.12) but they are applied so that a greater number of structures (i.e. those between 10 and 40 um in addition to those greater than 40 um) are included within the concentration that is assigned the greater potency value.

Despite the compromises adopted to define and apply C_{asb}, the analyses reported in Sections 6.2.4.2 and 6.3.3.2 of this document indicate that it indeed represents an improved index of exposure over the index in current use by EPA, C_{PCME}, apparently because it better captures the characteristics of asbestos that determine biological activity than the current index (Section 7.5). The analyses presented in Sections 6.2.4.2 and 6.3.3.2 demonstrate that, when human dose-response coefficients are adjusted to match the exposure expressed as C_{asb}, the variation observed in the published values across studies is reduced in comparison to unadjusted coefficients (which are matched with C_{PCME}).

Remarkably, the improved across-study agreement observed when risk coefficients are adjusted to C_{asb} is achieved despite the limitations of the manner in which the coefficients are adjusted, including:

- that the definition of C_{asb} itself is a compromise that does not fully account for the effects of structure size. The optimum exposure index recommended in Section 7.5 of this document (Equation 7.12) could not be applied to the epidemiology studies because available TEM size distributions would not support it (Section 6.2.4.2). Therefore, as indicated above, the length dimensions of the longest size category incorporated into C_{asb} is substantially shorter than what is considered optimal;

- that the size distributions employed to adjust risk coefficients to match C_{asb} were obtained from analyses performed in separate studies than those from which the corresponding risk coefficients were derived. Thus, the size distributions employed for the adjustments were typically derived under time-frames and conditions that differed from those that obtained during the studies from which the risk coefficients were derived, even if such studies were conducted in the same facility (which was not always the case);

- that the same size adjustment was applied to each of the multiple risk coefficients representing a particular fiber type in a particular type of industrial setting (e.g. chrysotile in textile production) even when such risk coefficients were derived from studies at different facilities, which would typically exhibit somewhat varying conditions; and

- that each risk coefficient was subjected to a single, average adjustment for fiber size despite the fact that each such coefficient was derived from a long-term study during which exposure conditions (potentially including fiber size distribution) typically changed substantially over the course of the study.

Due to the limitations described above, a small number of follow-on studies are recommended in the text of this document (Chapter 8), which would provide the additional data required to allow use of a better optimized exposure index and may reduce some of the uncertainty associated with use of generic-industry-based adjustments rather than study-specific adjustments.

As a further test of the relative performance of the recommended, interim index (vs. the index in current use), we compared the ability of the interim index (C_{asb}) and the current index (C_{PCME}) to fit (predict) the relative tumorigenicity of six tremolite samples that were intraperitoneally injected into rats in a study by Davis et al. (1991). This is a study to evaluate the relative tumorigenicity of tremolite samples that vary primarily by the difference in the degree of their "asbestiform character" (i.e. the difference in the degree that each contains asbestos-type fibers vs cleavage fragments of acicular tremolite).

The data from this study were selected for evaluation for two reasons:

(1) because the published study includes detailed bivariate size distributions for each of the samples, which allows us to derive concentration estimates based on each of the exposure indices of interest; and

(2) because the study provided an opportunity to evaluate the importance of considering the degree of "asbestiform character" of a sample when analyzing such samples for risk assessment.

The data used to develop estimates of the magnitude of the response (i.e. frequency of tumors) and the magnitude of the dose injected for each sample in the Davis et al. study, based on the current index of exposure, C_{PCME}, is provided in Table B-1. The first column of the Table indicates the identification of the sample. The second and third columns, respectively, provide the number of animals dosed and the number of mesotheliomas observed. The fourth column is an estimate of the rate of mesotheliomas observed for each sample tested (equal to the number of animals with tumors divided by the number of animals dosed). Columns five and six provide, respectively, estimates of the upper bound and lower bound mesothelioma rates for each sample (derived assuming that the observed frequency of mesotheliomas among the population of dosed animals is binomially distributed).

Table B-1

Columns seven and eight of Table B-1 present, respectively, the mass dose administered and the estimated number of PCME fibers administered to each animal for each sample. Columns 9 and 10 (the last two columns of the table) present, respectively, the upper and lower confidence bounds on the estimated number of fibers in each sample dose. These confidence bounds are derived assuming that the number of fibers observed in each sample is Poisson distributed.

The fit of the estimated doses (based on PCME) to the observed tumor incidence is provided in Figure B-1. In this figure, the observed mesothelioma incidence is plotted on the Y-axis and the estimated PCME dose is plotted on the X-axis. The solid squares are points representing the observed tumor incidence and the best estimate of average dose for each experiment. The hollow rectangles surrounding each solid square represent the estimated confidence bounds for each point (i.e. the confidence bounds for tumor incidence on the vertical axis and the confidence bounds for dose on the horizontal axis). The curve in the figure represents the best-fit dose-response model (which has the same form as that described to evaluate the Davis et al. inhalation data (Equation 7.7, Section 7.4.3), except that the symbols have been changed and the equation simplified for this application:

$$I_M = 1 - \exp(\alpha - \beta d) \qquad \text{(B.1)}$$

where:

I_M is the observed incidence of mesotheliomas in each experiment;

α is a coefficient used to adjuste for any estimated background rate of mesotheliomas among unexposed rats;

β is a coefficient representing the potency for PCME fibers; and

d is the estimated dose of PCME fibers.

Because background rates from an appropriate control population was not provided in this paper, the background incidence of mesothelioma was optimized as an adjustable parameter. The fits of this model to the data was optimized visually by trial and error. In this case, the best estimate model indicates a background mesothelioma incidence rate, $\alpha = 0$ and an estimated potency coefficient, $\beta = 0.004$.

Figure B-1

As is obvious from the figure, the fit is entirely inadequate, as the "best fit" line does not even touch two of the six hollow boxes in the figure. Moreover, it should be obvious from the relative location of the hollow boxes representing the samples with the three lowest tumor responses in this figure, that no smooth dose-response curve can be constructed that can pass through all three of these boxes. Therefore, it is not possible to fit these data using this index.

In comparison, the data used to develop estimates of the magnitude of the response (i.e. frequency of tumors, which is the same as in Table B-1) and the magnitude of the dose injected for each sample in the Davis et al. study, based on the interim index of exposure, C_{asb}, is provided in Table B-2. The information provided in each of the columns of Table B-2 is the same as the information provided in the corresponding column from Table B-1.

In further comparison, the fit of the estimated doses (based on the interim index recommended in this document) to the observed tumor incidence is provided in Figure B-2. The format for this figure is identical to that described for Figure B-1. The best fit of the model to the observed mesothelioma incidence in these experiments using the interim index indicates a coefficient for the background rate, $\alpha = 0$ and an estimated potency coefficient, $\beta = 0.19$. That the resulting curve passes well within the boundaries of the hollow boxes for each of the six samples indicates that this model provides an adequate fit to these data.

Note that the appearance that the boxes representing the confidence intervals in this figure are larger than in Figure B-1 is an artifact created by the difference in the scales of the two figures. Because the magnitude of the doses for the interim index are smaller than those for PCME, the X-axis scale in Figure B-2 is expanded relative to Figure B-1. Thus the boxes appear wider in Figure B-2.

When dose is expressed in terms of the interim index recommended in this document, the observed tumor incidence for the six tremolite samples studied by Davis et al. (1991), each with vastly differing degree of asbestiform character, can be adequately predicted. This means, among other things, that it is not necessary to distinguish fibers from cleavage fragments when evaluating potency using the recommended, interim index. All structures that exhibit the requisite dimensions, whether asbestiform or not, should be included in the count.

In contrast, doses estimated using the current EPA index cannot predict the relative potency of these six tremolite samples. Whether, by adjusting the dose estimates for the fraction of asbestiform fibers vs. cleavage fragments might improve the fit remains to be seen. The data provided in the paper were not sufficient to allow for such adjustments. Even if it were, this additional complication, which is not beyond

Table B-2

Figure B-2

controversy, makes use of the current EPA index even less favorable relative to use of the recommended interim index, in addition to the reasons stated in Section 7.5 and the beginning of this appendix.